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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,564	05/12/2006	Jianliang Lu	X16541	5512

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EXAMINER	
CHANDRAKUMAR, NIZAL S	
ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
03/19/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No.	Applicant(s)	
	10/579,564	LU ET AL.	
	Examiner	Art Unit	
	NIZAL S. CHANDRAKUMAR	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 20-22* is/are pending in the application.

4a) Of the above claim(s) *2,16,17 and 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I claims 1, 3-15 in the reply filed on 01/28/2008 is acknowledged.

Claims 1-17, 20-22 are pending.

Claims 2, 16-17, 20-22 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 01/28/2008.

This application contains claims 2, 16-17, 20-22 drawn to an invention nonelected with traverse in the reply filed on 01/28/2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

It is noted that in the office action filed 12/27/2007 Examiner requested Election of species with respect to variables LTB, LP1 and LP2. The applicant did not elect a species.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, 3-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are drawn to ester prodrugs without defining the chemical structures of the prodrug compounds being claimed. What are the structures of these "prodrugs"? Applicants' "prodrugs" are molecules whose structure lie outside the subject matter of formula I, but upon metabolism in the body are converted to active compounds falling within the structural scope of formula I. The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrugs". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claims. Attempting to define means by functions is not proper when the means can be clearly expressed in terms that are more precise.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a limited number of compounds of the formula, does not reasonably provide enablement for the plurality of possible structures claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The specification is enabling for a limited number of possibilities for the substituents of the elected groups of compounds. The specification, *for example*, while enabling for making compounds wherein R = R' = ethyl and Lp1 = O, is not enabling for making other zillion possibilities claimed. It is not seen, *for example*, where in the specification, enabling disclosure for making or using (biological activity) a compound wherein RT3 is other than H. Further, it is not seen where enabling disclosrue for prodrugs is present in the specification for compounds of formula I; what is

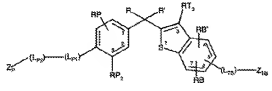
discussed is academic teachings about prodrugs.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the relevant factual considerations.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art.

All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

The breadth of the claims: The elected group I is drawn to compounds of the following formula

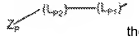


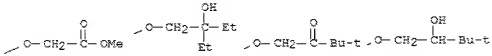
wherein the independently varying substituents (layered on top of substituents) are defined over 20 pages encompassing zillions of compounds. These compounds encompass molecules that widely vary in the physical and chemical properties such as size, molecular weight, logP, acidity and basicity, properties that are known in the art to greatly influence the PK and PD parameters that are relevant for the use aspect of the claimed invention. Further, the claims are also drawn to prodrugs of undefined chemical structures rendering the breadth and scope of the claims large that is not supported by the disclosure in the specification.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in

the art of organic and medicinal chemistry, it is noted that each embodiment of the invention is required to be individually assessed for viability.

The amount of direction provided by the inventor and the presence or absence of working examples:

With respect to variables  the disclosure is limited to the following (chemistry predicating the limitation, see below).



of which the first and third moieties are precursors to the second and fourth moieties respectively.

With regards to variables R, R', the direction and working example provided in the specification is limited to making compounds wherein R = R' are (the same) ethyl groups. However, the disclosed method of making these substituents would be applicable to making compounds wherein R and R' are alkyl groups or form a carbocycle as long as these substituents are unfunctionalized alkyl groups, that is groups compatible with the chemistry needed to introduce these groups (see below).

With regards to variable RP, the disclosure is limited to H.

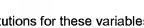
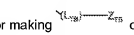
With regards to variable RP3, the disclosure is limited methyl group, thus enabling for groups that would not participate in Grignard reactions or the Lewis acid catalyzed (carbenium ion forming) reactions.

The quaternary center forming, carbenium ion quenching reaction dictates that Lp1-aryl bond is O-aryl bond.

Likewise, the above mentioned, carbon-carbon bond forming reactions, would not be compatible with groups such as acetyl, alkenyl etc. In addition, while an electron donating RP(3) substituent could facilitate reaction with carbenium ion, the same can not be said for a RP(3) electron withdrawing substituent.

With regards to the RB and RB', the specification is limited to halo, hydroxyl and carboxylic acid substituents. The variables RB, RB' and RT3 are limited by the availability of functionalized

benzaldehydes and functionalized mercapto acetic acids, suitably protected (see below), and compatibility of these functionalities for the reaction protocols disclosed in the specification or in the prior art. Thus, for example, the making of RT3 substituent to be bromo or nitro, would require either the corresponding mercapto acetic acid or the ability to introduce these substituents after the formation of the benzothiophene ring systems. The guidance and direction provided in the specification are lacking to meet these uncertainties. For example, the specification does not provide citations (commercial or literature) for procuring the starting materials usable that could substitute for the lack of working examples with respect to non-enabled substitutions for these variables.

For reasons similar to substituents on the isolated benzene ring, it is not seen where in the specification enablement is found for making  other than, hydroxyl, alkoxy or carboxylic acid, carboxylic acid esters and carboxamides. The disclosure is limited to making amides from these carboxylic acids, but there is no direction, guidance or working examples for making the plethora of groups claimed for  with respect to making or using.

The specification lacks guidance for making or using prodrugs. (see rejection under 35 U.S.C. 112, second paragraph). The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo,* this is still an experimental science. It is well known in the art that for a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large degree of experimentation. The disclosure relating to these tests is lacking in the specification.

The state and the predictability of the art: With regards to making of the compounds, in spite of major advances in protecting group strategies in synthesis, the state of the art is unpredictable as to functional group compatibility during many chemical transformations. *For instance*, as explained above, the feasibility of any conceivable reaction scheme for the preparation of an instantly claimed variables such as RP and RP3 would be unpredictable because what has been taught in the specification and in the prior art, at the time of the instant application, is for making benzene ring substituent that is inert to reaction conditions that are necessary to form the quaternary center. Likewise, the RP and RP3 substituents have to be compatible with reactions needed for introducing other variables present in the formula. Many of the claimed substituents in the instant case are not compatible with the chemistry taught in the specification such that undue experimentation would be required to arrive at viable synthetic strategies. The existence of such unpredictabilities and uncertainties would prevent one of ordinary skill in the art from accepting the process such as the one shown for minimally substituted benzene ring and unsubstituted R and R' alkyl groups, on its face as universally applicable for all the substitutions claimed.

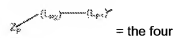
The quantity of experimentation: For the reasons presented above, there is a substantial gap between what is taught in the specification and what is being claimed. Based on the disclosure in the copending applications (10/578991, 10/515403, 10577967, 10579563) it is clear that many of the substituents need to remain the same (optimized) for productive interaction with Vitamin D receptor, even when the heterocyclic portions are modified. Thus, given that the specification(s) disclose(s) biological activity for limited number of narrowly defined variables such as compounds with R=R'=ethyl, one skilled in the art of medicinal chemistry would be faced with undue experiment to identify other specific embodiments encompassed by the formula, that would provide desirable biological activity.

It is suggested that the term 'prodrugs' is deleted from the claims.

The specification is enabling for,

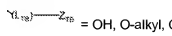
RP= H

RP3 = unsubstituted (i.e., unfunctionalized lower alkyl)

 = the four moieties shown above, of which, the alkyl groups could be lower alkyl;

RT3 = H

RB = RB' = H

 = OH, O-alkyl, COOH, COO-lower alkyl, carboxamides.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, one of ordinary skill in the art would have to engage in undue experimentation to make and use the claimed invention.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIZAL S. CHANDRAKUMAR whose telephone number is (571)272-6202. The examiner can normally be reached on 8.30 AM - 4.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571 0272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nizal S. Chandrakumar

/D. Margaret Seaman/

Primary Examiner, Art Unit 1625